Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis

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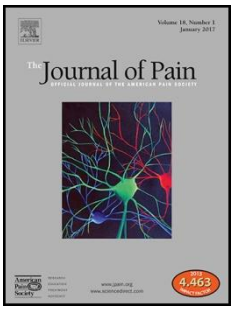
DOI: https://doi.org/10.1016/j.jpain.2017.11.005

Originally published at:
Vickers, Andrew J; Vertosick, Emily A; Lewith, George; MacPherson, Hugh; Foster, Nadine E; Sherman, Karen J; Irnich, Dominik; Witt, Claudia M; Linde, Klaus; Acupuncture Trialists' Collaboration (2018). Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. Journal of Pain, 19(5):455-474.
DOI: https://doi.org/10.1016/j.jpain.2017.11.005

Accepted Manuscript



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PII: S1526-5900(17)30780-0
DOI: https://doi.org/10.1016/j.jpain.2017.11.005
Reference: YJPAI 3487

To appear in: *The Journal of Pain*

Please cite this article as: Andrew J. Vickers, Emily A. Vertosick, George Lewith, Hugh MacPherson, Nadine E. Foster, Karen J. Sherman, Dominik Irnich, Claudia M. Witt, Klaus Linde, on behalf of the Acupuncture Trialists' Collaboration, Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis, *The Journal of Pain* (2017), https://doi.org/10.1016/j.jpain.2017.11.005.

Acupuncture for chronic pain: update of an individual patient data meta-analysis

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Authors' contributions

The study was conceived by AV, GL, CW and KL. AV was responsible for the overall study design; EV for the systematic review; GL and HM with respect to acupuncture analyses; CW, NF, KS and KL with respect to clinical trial methodology and meta-analysis. Statistical analyses were conducted by EV. The first draft of the manuscript was written by AV and EV. All authors gave comments on early drafts and approved the final version of the manuscript. AV had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. GL died between completion of the first draft of the manuscript and submission to this journal.

Disclosures

An ethics statement was not required for this work. The authors declare that they have no competing interests. The Acupuncture Trialists' Collaboration is funded by an R21 (AT004189I and an *R01* (AT006794) from the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of

Health (NIH) to Dr. Vickers) and by a grant from the Samueli Institute. Dr. MacPherson's work on this project was funded in part by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research scheme (RP-PG-0707-10186). Prof. Foster, an NIHR Senior Investigator, was supported through an NIHR Research Professorship (RP-011-015). The views expressed in this publication are those of the author(s) and not necessarily those of the NCCAM, NHS, NIHR or the Department of Health in England. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Highlights

- Acupuncture has a clinically relevant effect on chronic pain that persists over time
- The effect of acupuncture cannot be explained only by placebo effects
- Factors in addition to the specific effects of needling are important contributors
- Referral for acupuncture treatment is a reasonable option for chronic pain patients

Abstract

Despite wide use in clinical practice, acupuncture remains a controversial treatment for chronic pain. Our objective was to update an individual patient data meta-analysis to determine the effect size of acupuncture for four chronic pain conditions.We searched MEDLINE and the Cochrane Central Registry of Controlled Trials randomized trials published up until December 31, 2015. We included randomized trials of acupuncture needling versus either sham acupuncture or no acupuncture control for non-specific musculoskeletal pain, osteoarthritis, chronic headache, or shoulder pain. Trials were only included if allocation concealment was unambiguously determined to be adequate. Raw data were obtained from study authors and entered into an individual patient data meta-analysis**.** The main outcome measures were pain and function. An additional 13 trials were identified, with data received for a total of 20,827 patients from 39 trials. Acupuncture was superior to both sham and no acupuncture control for each pain condition (all $p<0.001$) with differences between groups close to 0.5 standard deviations (SD) for comparison with no acupuncture control and close to 0.2 SDs in comparison with sham. We also found clear evidence that the effects of acupuncture persist over time with only a small decrease, approximately 15%, in treatment effect at one year. In secondary analyses, we found no obvious association between trial outcome and characteristics of acupuncture treatment, but effect sizes of acupuncture were associated with the type of control group, with smaller effects sizes for sham controlled trials that used a penetrating needle for sham, and for trials that had high intensity of intervention in the control arm.We conclude that acupuncture is effective for the treatment of chronic pain, with treatment effects persisting over time. While factors in addition to the specific effects of needling at correct acupuncture point locations are important contributors to the treatment effect, decreases in pain following acupuncture cannot be explained solely in terms of placebo effects. Variations in the effect size of acupuncture in different trials are driven predominately by differences in treatments received by the control group rather than by differences in the characteristics of acupuncture treatment.

Perspective

Acupuncture is effective for the treatment of chronic musculosketal, headache and osteoarthritis pain. Treatment effects of acupuncture persist over time and cannot be explained solely in terms of placebo effects. Referral for a course of acupuncture treatment is a reasonable option for a patient with chronic pain.

Keywords: Acupuncture, chronic pain, meta-analysis, osteoarthritis, back pain, neck pain, migraine, tension-type headaches, shoulder pain

Introduction

Acupuncture remains a controversial treatment for chronic pain, largely due to a provenance outside biomedicine. Traditional acupuncture theory invokes non-anatomical structures such as meridians and non-physiological processes such as the flow of *qi* energy. Although many contemporary practitioners do not rely on such concepts, there remains a dearth of data on how insertion of needles at specific points on the body could lead to long-term decreases in pain. Acupuncture undoubtedly has short-term physiological effects, several of which are relevant to pain[7, 76, 119], but there is as yet no explanation as to how such effects could persist.

We previously reported an individual patient data meta-analysis of high-quality trials of acupuncture for chronic pain.[92] Differences between acupuncture and control in trials without sham (placebo) control were both statistically and clinically significant. Acupuncture was significantly superior to sham control, suggesting that acupuncture effects are not solely explicable in terms of placebo, although these differences were relatively modest. We have separately reported secondary analyses examining whether characteristics of acupuncture treatment[65] or control groups[68] influence effect size, and whether the effects of acupuncture treatment persist over time[69]. Here we update our prior analyses now including studies published during the last 7 years.

Methods

The full protocol of the meta-analysis[93] and the results of the first individual patient data meta-analysis including RCTs published up to November 2008[92] have been published. The literature search was repeated to identify eligible RCTs published between December 2008 and December 2015. Trials were considered eligible if they accrued patients with nonspecific back or neck pain, shoulder pain, chronic headache, or osteoarthritis; pain duration was at least 4 weeks for musculoskeletal disorders; at least one group received acupuncture needling and one group received either sham acupuncture or no acupuncture control; the primary endpoint was measured more than 4 weeks after the initial acupuncture treatment; and allocation concealment was determined unambiguously to be adequate. Principal investigators of eligible studies were asked to provide raw data. These raw data were used to replicate all analyses published in the original RCT publication to ensure data accuracy. Each trial was reanalyzed by analysis of covariance with the standardized primary endpoint (scores divided by pooled standard deviation) as the dependent variable, and the baseline measure of the primary endpoint and variables used to stratify randomization as covariates. The primary outcome for each study was that identified by the responding author of each study. The effect sizes for each study were then entered into a meta-analysis using the *metan* command in Stata (version 13, StataCorp, College Station, TX). Both fixed effects and random effects estimates were calculated. Fixed effects weights were calculated using inverse-variance weighting, and random effects weights were calculated using the DerSimonian and Laird method. We pre-specified that meta-analyses would be conducted separately for comparisons of acupuncture vs. sham and acupuncture vs. no acupuncture control, and within each pain type, and the hypothesis test would be based on the fixed effects analysis. In

the original paper, trials for which individual patient data were not available were included as a sensitivity analysis; in this update, we include summary data for these trials in the main meta-analysis and exclude them as a sensitivity analysis.

As secondary analyses, we examined whether characteristics of acupuncture treatment modified treatment effects. Both trial-level and patient-level analyses were performed. For trial-level analyses, we used random-effects meta-regression to test the effect of each characteristic on the main effect estimate using the Stata command *metareg*. For patient-level analyses, we created a linear regression as for the main analysis of effect size, but included the characteristic and an interaction term between the characteristic and treatment allocation. The coefficient was then entered into a meta-analysis. In both analyses, random effects estimates and 95% confidence intervals were reported; p values are based on the fixed effects analysis. We also analyzed the effect of acupuncture relative to different types of sham acupuncture and different types of no acupuncture control group. Three comparisons of sham acupuncture were investigated: penetrating needle vs both non-penetrating needle and non-needle sham; non-penetrating needle vs non-needle sham; and the use of true acupuncture points vs non-acupuncture points among trials using non-penetrating or non-needle sham. For sham arms using penetrating needles, there was also a comparison done between the use of deep needle penetration and shallow needle penetration. We entered the effect size and standard error for each trial into a meta-regression along with the type of sham acupuncture used in that trial. For this analysis, smaller effect sizes indicate a smaller difference in effect between verum acupuncture and sham acupuncture, implying that the type of sham acupuncture used is more active and therefore more similar to verum acupuncture. For the analysis of acupuncture effect relative to no acupuncture control group, we used meta-regression to compare the effects of trials using no acupuncture control groups characterized as high intensity, usual care, or low intensity. We also repeated our prior analyses exploring possible effects of publication bias and exploring difference between sham acupuncture and no treatment.

Results

Systematic Review

Our systematic review[93] was updated to include trials published after November 2008 and before December 31, 2015. We identified 75 additional RCTs, of which 13 were eligible (Figure 1). These 13 studies include four trials[19, 56, 75, 85] included as summary data only in a sensitivity analysis in our first report.

Data Extraction and Quality Assessment

Individual patient data for 2,905 patients were received from 10 of these 13 studies and included patients from the United States, Australia, China, Germany and the UK. For one of the three studies for which we did not receive data, the statisticians involved in the RCT failed to respond to repeated enquiries despite approval for data sharing being obtained from the principal investigator. For the other two studies, the trial authors were contacted and invited to participate but we received no further response. These three studies were included in the analysis as summary data only using the published estimates of effect size.[31, 70, 75] Two trials from the original systematic review for which data were not received were also included as summary data in these analyses.[23, 74]

A total of 20,827 patients were included in the total 39 trials (Table 1). The trials comprised 25 comparisons with 16,041 patients of acupuncture and no acupuncture control, and 26 comparisons with 7,237 patients of acupuncture and sham acupuncture control. Of the trials on musculoskeletal pain, most had an eligibility criterion of a minimum 3 or 6 months pain duration. Amongst those for which individual patient data on chronicity were available, the median duration was 4 years (quartiles: 1.1 years, 10 years). There were two trials for which the time period between first symptom and evaluation of outcome could theoretically have been less than three months based on eligibility criteria and timing of assessment. For Irnich et al., the duration of disease was "4 – 52 weeks" for 19% of patients and longer than one year for the remainder.[41] In the case of Kleinhenz et al., no data were provided on chronicity, however, the indication was rotator cuff tendinitis, which is rarely treated in the acute phase.[52] We conclude that all but a trivial proportion of patients included in the analysis would have met the conventional definition of chronic pain, that is, pain lasting at least 3 to 6 months. Six sham RCTs were determined to have an intermediate likelihood of bias from unblinding.[13, 26, 41, 49, 59, 103] In one trial, two types of sham acupuncture were used, although only one type (non-needle sham acupuncture) was found to have an intermediate likelihood of bias from unblinding.[103] One trial (Hinman et al.) was determined to have a sham acupuncture arm with a high likelihood of bias from unblinding.[39] This trial was excluded from the main analyses comparing acupuncture to sham acupuncture, but a sensitivity analysis including this trial was performed. None of the 10 new trials included in this analysis had dropout rates of higher than 25%.

Meta-analysis

Forest plots for acupuncture against sham acupuncture and against no acupuncture control are shown separately for each of the 4 pain conditions in Figure 2 and Figure 3. Fixed effects weights are reported in Figures 2 and 3; forest plots with random effects weights reported are presented in Figures S1 and S2 of the supplementary materials. Meta-analytic statistics are shown in Table 2. Consistent with the results of the originally published meta-analysis, acupuncture is found to be statistically superior to control for all analyses ($p < 0.001$). Effect sizes in the updated analyses are similar to those in the original analyses, with effect sizes changing by 0.02 or less for most comparisons. Effect sizes are close to 0.5 in comparison to no acupuncture control and 0.2 for comparisons with sham. To illustrate these effect sizes in more

clinically applicable terms, if baseline pain score in a typical RCT was 60 on a scale of 0-100, with a standard deviation of 25, follow-up scores might be 43 in a no acupuncture control group, 35 in a sham acupuncture group, and 30 among true acupuncture patients. If response were defined as a pain reduction of 50% or more, response rates would be approximately 30%, 42.5% and 50%, respectively. Also in keeping with the original analyses, significant heterogeneity was found in 5 out of 7 comparisons. Significant heterogeneity remained for sham-controlled musculoskeletal pain and osteoarthritis ($p=0.001$ and $p<0.001$, respectively) even after excluding the outlying Vas et al. trials. There was also significant heterogeneity for all indications in the comparison of acupuncture with no acupuncture control. Heterogeneity is further explored below ("Modifiers of Trial Outcome").

Sensitivity Analyses

Prespecified sensitivity analyses are also shown in Table 2. The exclusion of the RCTs by Vas et al.[89-91] repeats our prior finding that the effect sizes for comparison with sham are similar for musculoskeletal pain, osteoarthritis and chronic headache. However, there are now sufficient trials for a meta-analysis of shoulder pain trials without inclusion of Vas et al.[90] and the effect size for this indication is clearly much greater. There is also a large effect size for sham controlled neck pain trials when these are analyzed separately from back pain. Most other sensitivity analyses had little impact on the main findings. Analyses incorporating assessment of patient blinding, missing data or trials without individual patient data, all had very similar results to the primary analysis. As the primary outcome included in the analysis was the outcome specified by the trial authors, we also performed a sensitivity analysis restricted to a single endpoint (pain intensity) at a fixed follow-up time (2 – 3 months after randomization). Results were again very similar apart from sham-controlled trials of musculoskeletal pain (Table 3), where effect size decreased from 0.30 to 0.13, but this appears to be attributable to there being only 5 out of 11 trials that measured pain intensity at 2-3 months, and the trials excluded happened to be those with the larger effect sizes.

We combined all trials into one meta-analysis for all indications to assess the possible effect of publication bias. As in the original analyses, we found some evidence that smaller studies had larger effect sizes for the sham comparison (p=0.024), but not for the no acupuncture comparisons (p=0.75). No significant asymmetry was seen after excluding the Vas trials and shoulder pain trials from the sham comparison (N=21, p=0.13), and also when excluding any trials with fewer than 100 patients (N=21, p=0.069). We found that the difference between acupuncture and control would become non-significant only if there were 51 and >100 unpublished trials with 100 patients and effect sizes in favor of control of 0.25 SD for sham and no acupuncture control respectively.

We also repeated our exploratory analysis comparing sham control with no acupuncture control. In a meta-analysis of 12 RCTs that had both sham and no acupuncture control arms, the effect sizes for sham were 0.39 (95% CI 0.33, 0.45) and 0.45 (95% CI 0.29, 0.61) for fixed and random effects, respectively (p<0.0001 for tests of both effect and heterogeneity).

Modifiers of trial outcome

In addition to updating the primary analyses, we also updated previously published analyses on how characteristics of the acupuncture and control interventions influence trial outcomes. Trial-level and patient-level characteristics are found in Tables 4 and 5, respectively.

Acupuncture Characteristics Analysis

We updated previously reported analyses examining whether characteristics of acupuncture treatment modified the effect of acupuncture relative to control. These analyses include both trial-level analysis, based on characteristics described in the study protocol, and patient-level analyses, based on data related to the individual patient. The results are shown in Table 6. We did not find any obvious association between trial outcome and characteristics such as the style of acupuncture (Traditional or Western), use of fixed versus individualized point selection or the use of electrical stimulation. The only clear finding was a dose-response effect to number of acupuncture treatments in trials with a no acupuncture control group (increase in effect size of 0.10 per five sessions, 95% CI -0.01, 0.21, p=0.001).

Sham Acupuncture Control Analysis

We also updated a previously published analysis looking at the effects of acupuncture relative to different types of sham acupuncture and no acupuncture control groups. Differences in effect between acupuncture and the different sham acupuncture groups are found in Table 7. The largest difference in effect between acupuncture and sham acupuncture was seen in trials using non-penetrating needles, while the smallest difference was seen in trials using needle penetration. Significant differences were found between trials using penetrating needle sham and those trials that used non-penetrating or non-needle sham (difference in SD -0.30, 95% CI -0.60, -0.00, p=0.047), although this result was sensitive to the exclusion of the outlying Vas trials (difference in SD -0.07, 95% CI -0.24, 0.10, p=0.4, Table 8), two of which used non-penetrating controls.

No Acupuncture Control Analysis

In addition to updating the analysis comparing types of sham acupuncture control, we also updated the analysis comparing types of no acupuncture control. We updated the categorization of no acupuncture control groups, and categorized trials as having a high intensity, usual care, or low intensity control group. In a “high intensity” control group, patients received a specified course of protocol-guided treatment. For instance, the UK APEX trial by Foster et al.[33] is considered a high intensity control because patients were randomized to receive a course of individualized, supervised physical therapy plus acupuncture vs. physical therapy alone. In a trial with “usual care” control, patients are able to access whatever care they might reasonably receive outside of the study. As an example, in the UK NHS study, patients were randomized to "use" vs. "avoid" acupuncture and could receive whatever other treatments were offered to them.[95] A control group was defined as “low intensity” if patients were not allowed to receive certain treatments that might otherwise be available. For instance, the Acupuncture Randomized Trials for low back pain and osteoarthritis limited treatment of pain in the control group to oral nonsteroidal anti-inflammatory drugs, excluding other types of treatment, such as steroids and other classes of analgesics.[11, 108] Trials were assessed and assigned a control group type by three collaborators, with disagreements resolved by consensus. One trial was excluded from this analysis as there was a reasonable argument that it involved active control, prespecified to be excluded.[26] Differences in effect between acupuncture and no acupuncture control groups are presented in Table 7. Significant differences were found between

acupuncture and control for all types of no acupuncture control group. Notably, however, in trials that had high intensity control groups, acupuncture had smaller effect sizes compared to those with low intensity controls groups (difference -0.81, 95% CI -1.26, -0.36, p=0.0004); similarly in trials with usual care control acupuncture had smaller effect sizes than trials with a low intensity control group (difference in SD -0.65, 95% CI -0.98, -0.31, p=0.0002, Table 8).

Time Course of Acupuncture Effects Analysis

We updated a previously published analysis assessing change in the effects of acupuncture over time relative to sham acupuncture and no acupuncture control[69]. Number of weeks of acupuncture treatment and the time points used in this analysis are reported in Table 9. A total of 14 trials and 4,124 patients were included in the analysis of acupuncture vs no acupuncture control. The fixed-effects estimate for the between-group comparison of acupuncture vs no acupuncture controls showed a decrease in the effect size of acupuncture of 0.019 SD per 3 months (95% CI -0.041, 0.003, p=0.096, p=0.011 for heterogeneity, Figure 4a). Given a difference between acupuncture and no acupuncture control of around 0.5 SD, this is equivalent to about a 15% decrease in acupuncture effect relative to control at 1 year after randomization, which was usually between 9 and 10 months after the end of treatment. In the analysis of acupuncture vs sham acupuncture, a total of 21 trials and 6,276 patients were included. There was a non-significant decrease of 0.012 SD per 3 months in acupuncture relative to sham acupuncture (95% CI -0.035, 0.011, p=0.3, Figure 4b), about a 25% decrease in acupuncture effect at 1 year after randomization. Significant heterogeneity among trials was seen (p<0.0001). The previous analysis found that the decrease in effect of acupuncture relative to sham was driven by the decrease in neck pain trials (a decrease of 0.587 SD per 3 months, 95% CI -0.767, -0.406, p<0.0001). We also analyzed the change in acupuncture relative to sham excluding these trials and found a non-significant decrease of -0.003 SD per 3 months (95% CI -0.026, 0.020, p=0.8) with no significant heterogeneity among trials (p=0.12). Hence almost all the decrease in acupuncture effects in this analysis seems attributable to neck pain.

As a sensitivity analysis, we repeated the analyses including only trials that found a significant difference between acupuncture and control, as trials that showed no difference between groups cannot show a reduction in acupuncture effects over time. Nine trials with 2,997 patients were included in this analysis for the comparison between acupuncture and no acupuncture controls. A smaller and still non-significant decrease in the effect of acupuncture was found (-0.008 SD per 3 months, 95% CI -0.034, 0.018, p=0.5) and heterogeneity between trials was reduced (p=0.082). None of the newly included trials showed a significant effect of acupuncture vs sham and so this analysis of sham-controlled trials with a significant effect contains the same 7 trials and 1,450 patients and has the same results as reported in the original publication (-0.049 SD per 3 months, 95% CI -0.086, -0.013, p=0.008, heterogeneity p<0.0001).

Discussion

We updated an individual patient data meta-analysis of high-quality trials of acupuncture for chronic pain with seven additional years of data. An additional 10 studies were included with nearly 3,000 patients. In total, our analyses include 39 studies and 20,827 patients. The results confirm and strengthen prior key findings that acupuncture has a clinically relevant effect compared to no acupuncture control. Moreover, we confirmed that, although the effects of acupuncture are not completely explicable in terms of placebo effects, factors other than the specific effects of needling at correct acupuncture point locations are important contributors to acupuncture treatment benefit. Effects of acupuncture appear to persist over at least a 12 month period.

Heterogeneity continues to be an obvious aspect of our findings, with the results of trials varying by more than would be expected by chance. We have presented data that heterogeneity is predominately driven by differences between control groups rather than by differences between acupuncture treatment characteristics. We did not find any obvious differences between the results of trials depending on treatment characteristics such as style of acupuncture, duration of treatment sessions or training of acupuncturists. By contrast, we found evidence that effect sizes of acupuncture were smaller for sham-controlled trials with penetrating needles and for no acupuncture control trials where patients received high intensity care (e.g. a trial of acupuncture plus physical therapy vs. physical therapy alone). In some cases, heterogeneity was also driven by a set of outlying trials with large effect sizes. We have presented these analyses with and without the outlying trials to provide all necessary information for interpreting these results and drawing conclusions.

Another novel finding is the higher than average effects of acupuncture on upper body musculoskeletal pain. We now have sufficient data to conduct a meta-analysis for neck pain and for shoulder pain, even after exclusion of outlying trials. The effect sizes versus sham, 0.57 for shoulder and 0.83 for neck pain, were much larger than seen for low back pain, osteoarthritis and headache, although we also saw evidence that treatment benefits did not persist for neck pain.

Since publication of our results, there has been no substantive critique of our methodology in the peer-reviewed literature. The main issue under discussion seems to be whether the effect size of acupuncture is clinically relevant[94], specifically, whether clinical relevance is determined by the comparison with no acupuncture control or by comparison with sham. We have previously argued in favor of the former, on the grounds that the clinical decision made by a referring clinician in discussion with their patient is not between acupuncture and sham but between acupuncture and no acupuncture. Our argument is given the context of the excellent safety profile of acupuncture[66], evidence that the non-specific effects of acupuncture are particular to acupuncture and are not easily reproduced[46, 54] and evidence provided here and elsewhere[9] that some interventions used as sham acupuncture may be physiologically active.

It is also illustrative to compare our results to those of other interventions routinely used in clinical practice. For instance, in one meta-analysis of non-steroidal anti-inflammatory drugs (NSAIDs) for osteoarthritis of the knee, the

effect size for NSAIDs vs placebo for trials that did not preselect NSAID responders was 0.23;[10] for chronic low back pain, the effect size for NSAIDs is < 0.20[29].

We find several implications for research. In terms of the methodology of subsequent acupuncture trials for chronic pain, we find that the balance of evidence is to give a higher dose of acupuncture in terms of a greater number of treatments in trials without sham control. Although the nature of the control group in trials will naturally be driven by the research question, investigators should be aware of the evidence that control arms that incorporate a relatively intense level of intervention, such as when acupuncture is added into an intensive rehabilitation regimen, tend to lead to smaller effect sizes, as do sham controls that involve needle penetration. Further research is warranted on whether acupuncture is particularly effective for upper body musculoskeletal pain. An associated hypothesis is whether there are subtypes of other chronic pain indications that have differential response to acupuncture. It would naturally be ideal to know before referring a patient for treatment whether, say, the type of back pain they are experiencing is one that would be amenable to treatment with acupuncture. We will also repeat our prior call for research on how best to incorporate acupuncture into the multidisciplinary care of chronic pain patients.

In terms of implications for clinical practice, we have confirmed that acupuncture has a clinically relevant, persistent effect on chronic pain that is not completely explained by placebo effects. Referral for a course of acupuncture treatment is therefore a reasonable option for a patient with chronic pain.

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Figure 2. Forest plots for the comparison of acupuncture with no-acupuncture control. There were fewer than 3 trials for shoulder pain, so no meta-analyses were performed. Weights reported are fixed-effects weights calculated using inverse-variance weighting.

Figure 3. Forest plots for the comparison of true and sham acupuncture. Weights reported are fixed-effects weights calculated using inverse-variance weighting.

Figure 4. Forest plot showing the difference in pain change scores between acupuncture and no acupuncture control groups (a) and between acupuncture and sham acupuncture groups (b) over time. A coefficient of 0.01 means that the difference between acupuncture and control increases by 0.01 standard deviations for each 3 months following the end of treatment.

Supplementary Materials

Figure S1. Forest plots for the comparison of acupuncture with no-acupuncture control. There were fewer than 3 trials for shoulder pain, so no meta-analyses were performed. Weights reported are random-effects weights calculated using the DerSimonian and Laird method.

Figure S2. Forest plots for the comparison of true and sham acupuncture. Weights reported are random-effects weights calculated using the DerSimonian and Laird method.

Table 1. Characteristics of included studies

Indication (n=44)	Pain Type	Control Group	Primary Outcome Measure	Time Point
Chronic headache (n=9)	Migraine (n=3)[26, 59, 63], tension-type headache (n=3)[23, 28, 71], both[31, 43, 95] (n=3)	Sham control (n=5)[26, 28, 59, 63, 71] No acupuncture control (n=7); ancillary care (n=2)[23, 31]; usual care (n=4)[43, 63, 71, 95]; guideline care (n=1)[26]	Severity score (n=2)[23, 95]; days with headache (n=3)[28, 43, 71]; days with migraine (n=2)[26, 59]; days with moderate-to-severe pain (n=1)[63]; Migraine Disability Assessment (MIDAS) (n=1)[31]	1 mo (n=1)[23] 2 mo (n=1)[31] 3 mo (n=3)[43, 63, 71] 4 mo (n=1)[59] 6 mo (n=2)[26, 28] 12 mo (n=1)[95]
Nonspecific musculoskeletal pain (back and neck) (n=18)	Back (n=12)[11, 13, 18, 19, 36, 40, 48, 49, 74, 87, 102, 111]; neck (n=6)[41, 67, 79, 91, 104, 109]	Sham control (n=10)[11, 13, 19, 36, 41, 48, 49, 74, 91, 104]; No acupuncture control (n=12); Ancillary care (n=3)[40, 74, 102]; usual care (n=7)[11, 19, 67, 79, 87, 109, 111]; non-specific advice (n=1)[18]; guideline care (n=1)[36]	VAS (n=7)[11, 13, 41, 49, 74, 91, 104]; Roland Morris Disability Questionnaire (n=3)[18, 19, 48]; Northwick Park Neck Pain Questionnaire (n=2)[67, 79]; SF-36 Bodily pain (n=2)[87, 102]; Hannover Functional Questionnaire (n=1)[111]; Von Korff pain score (n=1)[36]; Oswestry Disability Index (n=1)[40]	1 mo (n=4)[41, 49, 91, 104] 2 mo (n=3)[11, 18, 19] 3 mo (n=5)[48, 74, 79, 109, 111] 4 mo (n=1)[102] 6 mo (n=2)[36, 40] 8 mo (n=1)[13] 12 mo (n=1)[67] 24 mo (n=1)[87]
Osteoarthritis (n=13)		Sham control (n=10)[8, 16, 33, 39, 70, 80, 85, 89, 103, 108] No acupuncture control (n=10); ancillary care (n=3)[33, 70, 80]; usual care (n=5)[39, 56, 85, 108, 110]; nonspecific advice (n=2)[8, 107]	WOMAC (n=5)[16, 56, 70, 108, 110]; WOMAC Pain subscore (n=4)[8, 33, 80, 89]; Oxford Knee score questionnaire (n=1)[107]; VAS[103] (n=1); knee pain (0-10) (n=1)[39]; Joint-specific Multidimensional Assessment of Pain (n=1)[85]	1 mo (n=1)[103] 2 mo (n=3)[70, 107, 108] 3 mo (n=6)[16, 39, 56, 85, 89, 110] 6 mo (n=3)[8, 33, 80]
Shoulder pain (n=4)		Sham control (n=4)[35, 52, 75, 90] No-acupuncture control (n=1); ancillary care (n=1)[75]	Constant-Murley score (n=2)[52, 90]; VAS (n=2)[35, 75]	1 mo (n=2)[52, 90] 6 mo (n=2)[35, 75]

Table 2. Primary Analyses, N=44 trials. Acupuncture is superior to control at p<0.001 except where indicated

		Sham				No acupuncture control			
Analysis	Indication	No. of studies	FE (95% CI)	Heterogeneity p-value	RE (95% CI)	No. of studies	FE (95% CI)	Heterogeneity p-value	RE (95% CI)
Main Analysis	Non-specific musculoskeletal pain	10	0.30 (0.21, 0.38)	p<0.001	0.49 (0.16, 0.81)	12	0.54 (0.50, 0.57)	p<0.001	0.50 (0.38, 0.63)
	Osteoarthritis	9	0.24 (0.17, 0.31)	p<0.001	0.45 (0.15, 0.75)	10	0.63 (0.56, 0.69)	p<0.001	0.74 (0.46, 1.01)
	Chronic headache	5	0.16 (0.08, 0.25)	p=0.4	0.16 (0.08, 0.25)	7	0.44 (0.39, 0.48)	p<0.001	0.56 (0.35, 0.76)
	Shoulder	4	0.57 (0.44, 0.69)	p=0.4	0.57 (0.44, 0.69)	0	No trials		
Exclusion of Vas trials	Non-specific musculoskeletal pain	9	0.19 (0.11, 0.28)	p=0.001	0.31 (0.13, 0.48)				
	Osteoarthritis	8	0.18 (0.10, 0.25)	p<0.001	0.35 (0.07, 0.62)				
	Shoulder	3	0.58 (0.42, 0.74)	p=0.2	0.61 (0.40, 0.81)				
Separate pain types	Back pain	7	0.17 (0.07, 0.26)	p<0.001	0.30 (0.08, 0.52)	9	0.46 (0.41, 0.50)	p<0.001	0.52 (0.37, 0.67)
	Neck pain	3	0.83 (0.64, 1.01)	p<0.001	0.82 (-0.11, 1.75)				
Excluding trials with summary data only	Non-specific musculoskeletal pain	9	0.27 (0.19, 0.35)	p<0.001	0.44 (0.11, 0.78)	11	0.53 (0.50, 0.56)	p<0.001	0.45 (0.33, 0.57)
	Osteoarthritis	8	0.19 (0.12, 0.26)	p<0.001	0.26 (0.04, 0.48)	9	0.59 (0.52, 0.65)	p<0.001	0.59 (0.37, 0.82)
	Chronic headache					5	0.43 (0.38, 0.47)	p<0.001	0.44 (0.24, 0.64)
	Shoulder	3	0.62 (0.46, 0.77)	p=0.4	0.62 (0.46, 0.77)				
Excluding trials with possible bias due to blinding	Non-specific musculoskeletal pain	7	0.28 (0.19, 0.37)	p<0.001	0.51 (0.09, 0.93)				
	Osteoarthritis	9	0.23 (0.16, 0.31)	p<0.001	0.44 (0.13, 0.75)				
	Chronic headache*	3	0.15 (0.03, 0.26)	p=0.15	0.12 (-0.05, 0.29)				
Including trials with high likelihood of bias due to blinding	Osteoarthritis	10	0.23 (0.17, 0.30)	p<0.001	0.42 (0.14, 0.70)				
Multiple imputation	Non-specific musculoskeletal pain	10	0.29 (0.21, 0.37)	p<0.001	0.49 (0.16, 0.81)	12	0.54 (0.50, 0.57)	p<0.001	0.51 (0.38, 0.63)
	Osteoarthritis	9	0.24 (0.17, 0.31)	p<0.001	0.45 (0.15, 0.75)	10	0.63 (0.57, 0.70)	p<0.001	0.74 (0.46, 1.01)
	Chronic headache	5	0.17 (0.08, 0.25)	p=0.4	0.17 (0.08, 0.25)	7	0.44 (0.40, 0.49)	p<0.001	0.55 (0.35, 0.75)
	Shoulder	4	0.56 (0.44, 0.69)	p=0.4	0.56 (0.44, 0.69)				
Excluding trials where both acupuncture and control groups received additional treatments	Non-specific musculoskeletal pain					10	0.54 (0.51, 0.57)	p<0.001	0.54 (0.40, 0.67)
	Osteoarthritis	4	0.21 (0.11, 0.31)	p=0.081	0.22 (0.07, 0.38)	7	0.70 (0.62, 0.78)	p<0.001	0.70 (0.47, 0.93)
	Chronic headache					5	0.43 (0.38, 0.47)	p<0.001	0.44 (0.24, 0.64)
	Shoulder	3	0.58 (0.42, 0.74)	p=0.2	0.61 (0.40, 0.81)				

*p=0.015

Table 3. Sensitivity analyses including only pain endpoints measured between 2 and 3 months after randomization.

		Sham				No acupuncture control			
Analysis	Indication	No. of studies	FE (95% CI)	Heterogeneity p-value	RE (95% CI)	No. of studies	FE (95% CI)	Heterogeneity p-value	RE (95% CI)
Main Analysis	Non-specific musculoskeletal pain	5	0.13 (0.01, 0.25)	p=0.005	0.23 (-0.03, 0.49)	9	0.60 (0.56, 0.64)	p<0.0001	0.47 (0.34, 0.61)
	Osteoarthritis	7	0.31 (0.23, 0.39)	p<0.0001	0.69 (0.24, 1.14)	9	0.73 (0.66, 0.80)	p<0.0001	0.88 (0.61, 1.15)
	Chronic headache	5	0.14 (0.06, 0.22)	p=0.4	0.14 (0.06, 0.22)	7	0.43 (0.38, 0.47)	p<0.0001	0.45 (0.27, 0.63)
	Shoulder	2	No meta-analysis						

Table 4. Trial-level acupuncture characteristics, N=39. Counts for point prescription sum to 40 because one trial had two acupuncture groups, with each group receiving acupuncture based on a different point prescription.

Style of Acupuncture	
Combination of traditional Chinese and Western	9 (23%)
Traditional Chinese techniques	23 (59%)
Western	7 (18%)
Point Prescription	
Fixed needle formula	9 (23%)
Flexible formula	18 (45%)
Individualized	13 (33%)
Location of needles	
Both Local and Distal Points	37 (95%)
Distal Points Only	2 (5.1%)
Electrical stimulation allowed	11 (28%)
Manual stimulation allowed	36 (92%)
Moxibustion allowed	6 (15%)
Other Adjunctive Therapies Allowed	8 (21%)
De Qi attempted (N=35)	33 (94%)
Acupuncture-specific patient practitioner interactions	16 (40%)
Minimum years of experience required	
No requirement specified (0 years)	14 (36%)
6 months to 2 years	7 (18%)
3-4 years	13 (33%)
5-9 years	3 (7.7%)
10 years	2 (5.1%)
Maximum number of sessions	
1-5	3 (7.7%)
6-10	19 (49%)
11-15	12 (31%)
16-20	1 (2.6%)
21-25	2 (5.1%)
26-30	2 (5.1%)
Frequency of sessions (mean number of sessions per week)	
0.88	1 (2.6%)
1	19 (49%)
1.43	1 (2.6%)
1.5	7 (18%)
1.67	1 (2.6%)
2	9 (23%)
5	1 (2.6%)
Mean duration of sessions, rounded to whole numbers (N=34)	
15-19 minutes	1 (2.9%)
20-24 minutes	11 (32%)
25-29 minutes	6 (18%)
30+ minutes	16 (47%)
Mean number of needles used (N=33)	
1-4	3 (9.1%)
5-9	11 (33%)

10-14	12 (36%)
15-20	7 (21%)

Table 5. Patient-level acupuncture characteristics, n=20,827.

Number of Sessions	
0	441 (2.1%)
1-5	515 (2.5%)
6-10	8003 (38%)
11-15	2065 (10%)
16-20	40 (0.2%)
21-30	15 (<0.1%)
Missing	1989 (10%)
Not reported	7759 (37%)
Average Session Duration	
2-15	163 (0.8%)
15-30	2668 (13%)
31-45	377 (1.8%)
46-60	25 (0.1%)
60+	1 (<0.1%)
Missing	896 (4.3%)
Not reported	16697 (80%)
Average Number of Needles	
2-5	22 (0.1%)
6-10	910 (4.4%)
11-15	762 (3.7%)
16-20	825 (4.0%)
21-25	199 (1.0%)
26+	30 (0.1%)
Missing	1621 (7.8%)
Not reported	16458 (79%)
Age of Physician/Acupuncturist	
30-35	298 (1.4%)
36-40	2119 (10%)
41-45	2630 (13%)
46-50	2407 (12%)
51-55	1701 (8.2%)
56-60	872 (4.2%)
60+	303 (1.5%)
Missing	368 (1.8%)
Not reported	10129 (49%)
Physician/Acupuncturist Sex	
Female	3626 (17%)
Male	7002 (34%)
Missing	70 (0.3%)
Not reported	10129 (49%)

Table 6. Results of univariate meta-regression analyses for the effect of acupuncture characteristics on acupuncture effect. β is an estimate of the change in the effect of acupuncture in terms of standardized difference compared to controls for each characteristic; a positive β indicates a larger effect of acupuncture compared to controls for trials. N is number of trials. The number of patients in the analysis and number of patients in included trials are given in parentheses where applicable.

	Sham acupuncture				No acupuncture control			
	N	β	95% CI	p value	N	β	95% CI	p value
Style of acupuncture	25				25			
Some TCM vs. Western only		-0.00	-0.49, 0.48	>0.9		0.10	-0.55, 0.74	0.8
TCM only vs. some Western		0.02	-0.38, 0.42	0.9		-0.07	-0.42, 0.28	0.7
Point prescription	25				25			
Fixed needle formula		Ref.		0.6		Ref.		0.075
Flexible formula		0.20	-0.21, 0.60			0.01	-0.45, 0.46	
Fully individualized		-0.01	-0.75, 0.73			-0.34	-0.79, 0.10	
Electrical stimulation allowed	25	0.32	-0.11, 0.75	0.14	25	-0.12	-0.50, 0.26	0.5
Manual stimulation allowed	25	0.26	-0.42, 0.95	0.5	25	-0.38	-0.99, 0.23	0.2
Moxibustion allowed		No trials allowed			25	-0.32	-0.71, 0.06	0.10
Other adjunctive treatment allowed	25	-0.04	-1.00, 0.92	0.9	25	-0.22	-0.59, 0.16	0.3
De qi attempted	25	0.29	-0.67, 1.24	0.6	21	0.74	-0.04, 1.52	0.063
Acupuncture-specific patient practitioner interactions allowed	25	-0.03	-0.50, 0.44	0.9	25	-0.05	-0.38, 0.28	0.8
Minimum experience required (years)	25	0.04	-0.05, 0.13	0.4	25	0.05	-0.03, 0.12	0.2
Maximum number of sessions (per 5 sessions)	25	-0.01	-0.23, 0.22	0.9	25	0.01	-0.12, 0.14	0.9
Patient-level analysis	5 (1317/ 1377)	0.09	-0.31, 0.48	0.7	5 (8036/ 10157)	0.10	-0.01, 0.21	0.001
Patient-level analysis, including Hinman trial	6 (1421/1517)	-0.03	-0.36, -0.30	0.9				
Frequency of sessions (per week)	25	-0.06	-0.29, 0.18	0.6	25	0.21	-0.22, 0.64	0.3
Duration of sessions (per 5 minutes)	25	0.06	-0.13, 0.25	0.5	20	-0.06	-0.25, 0.13	0.5
Patient-level analysis	6 (2863/2969)	0.01	-0.08, 0.09	0.9				
Number of needles used (per 5 needles)	25	0.05	-0.17, 0.27	0.6	19	0.16	-0.05, 0.38	0.13
Patient-level analysis	5 (2232/2317)	0.04	-0.08, 0.16	0.5				
Age of practitioner (per 5 years)								
Patient-level analysis					6 (9127/10550)	-0.01	-0.04, 0.02	0.5
Male practitioner								
Patient-level analysis					6 (9384/10550)	-0.07	-0.16, 0.02	0.084

Table 7. Differences in effect size (in SD) between acupuncture and sham acupuncture groups (N=25) and between acupuncture and no acupuncture control groups (N=24). Total number of sham acupuncture-controlled trials sums to 26 because one trial had two different types of sham acupuncture control.

Sham Acupuncture			
Type of Control Group	N	Effect Size (95% CI)	p value
Penetrating needle sham	11	0.17 (0.11, 0.22)	<0.0001
Excluding B blinding grades	9	0.16 (0.09, 0.24)	<0.0001
Non-penetrating needle and non-needle sham	15	0.48 (0.22, 0.74)	0.0003
Excluding B blinding grades	11	0.51 (0.16, 0.86)	0.004
Including Hinman trial	16	0.46 (0.21, 0.70)	0.0003
Excluding Vas trials	12	0.27 (0.10, 0.44)	0.002
Non-penetrating needle sham	10	0.52 (0.14, 0.91)	0.007
Excluding Vas trials	7	0.22 (-0.05, 0.49)	0.11
Non-needle sham	5	0.37 (0.21, 0.52)	<0.0001
Including Hinman trial	6	0.32 (0.18, 0.46)	<0.0001
True acupuncture points (no penetrating needle sham)	12	0.48 (0.15, 0.80)	0.004
Excluding B blinding grades	10	0.51 (0.12, 0.89)	0.010
Including Hinman trial	13	0.45 (0.15, 0.75)	0.003
Excluding Vas trials	10	0.25 (0.06, 0.44)	0.011
Non-acupuncture points (no penetrating needle sham)	3	0.52 (0.35, 0.69)	<0.0001
Excluding Vas trials	2	0.47 (0.13, 0.81)	0.007
No Acupuncture Control			
Type of Control Group	N	Effect Size (95% CI)	p value
High intensity	5	0.34 (0.11, 0.57)	0.003
Usual care and low intensity	19	0.56 (0.43, 0.69)	<0.0001
Usual care	17	0.50 (0.40, 0.60)	<0.0001
Low intensity	2	1.14 (0.71, 1.58)	<0.0001

Table 8. Differences in effect size between different types of control group. A negative effect size indicates that there is a smaller difference in effect between acupuncture and control for group 1 than for group 2, that is, the effect of control group 1 is more similar to verum acupuncture than the effect of control group 2.

Sham Acupuncture			
Group 1	Group 2	Effect Size (95% CI)	p value
Penetrating needle sham	Non-penetrating and non-needle sham	-0.30 (-0.60, -0.00)	0.047
Excluding B blinding grades		-0.33 (-0.72, 0.05)	0.088
Including Hinman trial		-0.28 (-0.57, 0.01)	0.061
Excluding Vas trials		-0.07 (-0.24, 0.10)	0.4
Non-penetrating needle sham	Non-needle sham	0.13 (-0.44, 0.70)	0.6
Including Hinman trial		0.18 (-0.34, 0.70)	0.5
Excluding Vas trials		-0.18 (-0.52, 0.17)	0.3
True acupuncture points, excluding penetrating needle sham	Non-acupuncture points, excluding penetrating needle sham	-0.02 (-0.70, 0.66)	0.9
Including Hinman trial		-0.05 (-0.71, 0.61)	0.9
Excluding Vas trials		-0.22 (-0.75, 0.30)	0.4
No Acupuncture Controls			
Group 1	Group 2	Effect Size (95% CI)	p value
High intensity	Usual care and low intensity	-0.23 (-0.50, 0.05)	0.11
High intensity	Low intensity	-0.81 (-1.26, -0.36)	0.0004
Usual care	Low intensity	-0.65 (-0.98, -0.31)	0.0002

Table 9. Trials with sham and no acupuncture control and time points assessed after the end of treatment

			Sham Acupuncture		No acupuncture control		
Trial Name	Pain Condition	Average Length of Treatment	Time Points after End of Treatment	Included in meta-analysis	Control patients offered acupuncture treatment (Crossover)	Time Points after End of Treatment	Included in meta-analysis
Carlsson 2001[13]	Low Back Pain	8 weeks	Weeks 5 and 18	Yes			
Chen 2013[16]	Osteoarthritis	12 weeks	End of treatment and week 14	Yes			
Endres 2007[28]	Headache	6 weeks	End of treatment and weeks 7 and 20	Yes			
Guerra de Hoyos 2004[35]	Shoulder	8 weeks	Weeks 5 and 18	Yes			
Irnich 2001[41]	Neck	3 weeks	Weeks 1 and 10	Yes			
Kennedy 2008[48]	Low Back Pain	5 weeks	End of treatment and week 7	Yes			
Kerr 2003[49]	Low Back Pain	6 weeks	None	No			
Kleinhenz 1999[52]	Shoulder	4 weeks	End of treatment	No			
Li 2012[59]	Migraine	4 weeks	End of treatment and week 4	Yes			
Vas 2004[89]	Osteoarthritis	12 weeks	Week 1	No			
Vas 2006[91]	Neck	3 weeks	Weeks 1 and 25	Yes			
Vas 2008[90]	Shoulder	3 weeks	Weeks 1 and 10	Yes			
White 2004[104]	Neck	4 weeks	End of treatment and weeks 1 through 8	Yes			
White 2012[103]	Osteoarthritis	4 weeks	End of treatment and week 1	Yes			
Berman 2004[8]	Osteoarthritis	26 weeks	End of treatment	No	No	End of treatment	No
Brinkhaus 2006[11]	Low Back Pain	8 weeks	End of treatment and weeks 18 and 44	Yes	At 8 weeks	End of treatment	No
Cherkin 2009[19]	Low Back Pain	7 weeks	Weeks 1, 19 and 45	Yes	No	Weeks 1, 19 and 45	Yes
Diener 2006[26]	Migraine	6 weeks	End of treatment and weeks 7 and 20	Yes	No	End of treatment and weeks 7 and 20	Yes
Foster 2007[33]	Osteoarthritis	3 weeks	Weeks 3, 23 and 49	Yes	No	Weeks 3, 23 and 49	Yes
Haake 2007[36]	Low Back Pain	6 weeks	End of treatment and weeks 7 and 20	Yes	No	End of treatment and weeks 7 and 20	Yes
Linde 2005[63]	Migraine	8 weeks	End of treatment and weeks 4 and 16	Yes	At 12 weeks	Week 4	No
Melchart 2005[71]	Headache	8 weeks	End of treatment and weeks 4 and 16	Yes	At 12 weeks	Week 4	No
Scharf 2006[80]	Osteoarthritis	6 weeks	Weeks 7 and 20	Yes	No	Weeks 7 and 20	Yes
Suarez-Almazor 2010[85]	Osteoarthritis	6 weeks	End of treatment and week 7	Yes	No	Week 7	No
Witt 2005[108]	Osteoarthritis	8 weeks	End of treatment and weeks 18 and 44	Yes	At 8 weeks	End of treatment	No

Cherkin 2001[18]	Low Back Pain	10 weeks			No	End of treatment and week 42	Yes
Hinman 2014[39]	Osteoarthritis	12 weeks			No	End of treatment and week 40	Yes
Hunter 2012[40]	Low Back Pain	6 weeks			No	Weeks 2, 7 and 20	Yes
Jena 2008[43]	Headache	12 weeks			At 12 weeks	All measurements after crossover	No
Lansdown 2009[56]	Osteoarthritis	10 weeks			No	Weeks 3 and 42	Yes
MacPherson 2015[67]	Neck	16 weeks			No	Weeks 10 and 36	Yes
Thomas 2006[87]	Low Back Pain	12 weeks			No	Weeks 1, 40 and 92	Yes
Salter 2006[79]	Neck	12 weeks			No	Week 1	No
Vickers 2004[95]	Headache	6 weeks			No	Weeks 1 and 40	Yes
Weiss 2013[102]	Low Back Pain	4 weeks			No	End of treatment and week 13	Yes
Williamson 2007[107]	Osteoarthritis	6 weeks			No	Weeks 1 and 6	Yes
Witt 2006[109]	Neck	12 weeks			At 12 weeks	All measurements after crossover	No
Witt 2006[110]	Osteoarthritis	12 weeks			At 12 weeks	All measurements after crossover	No
Witt ARC 2006[111]	Low Back Pain	12 weeks			At 12 weeks	All measurements after crossover	No

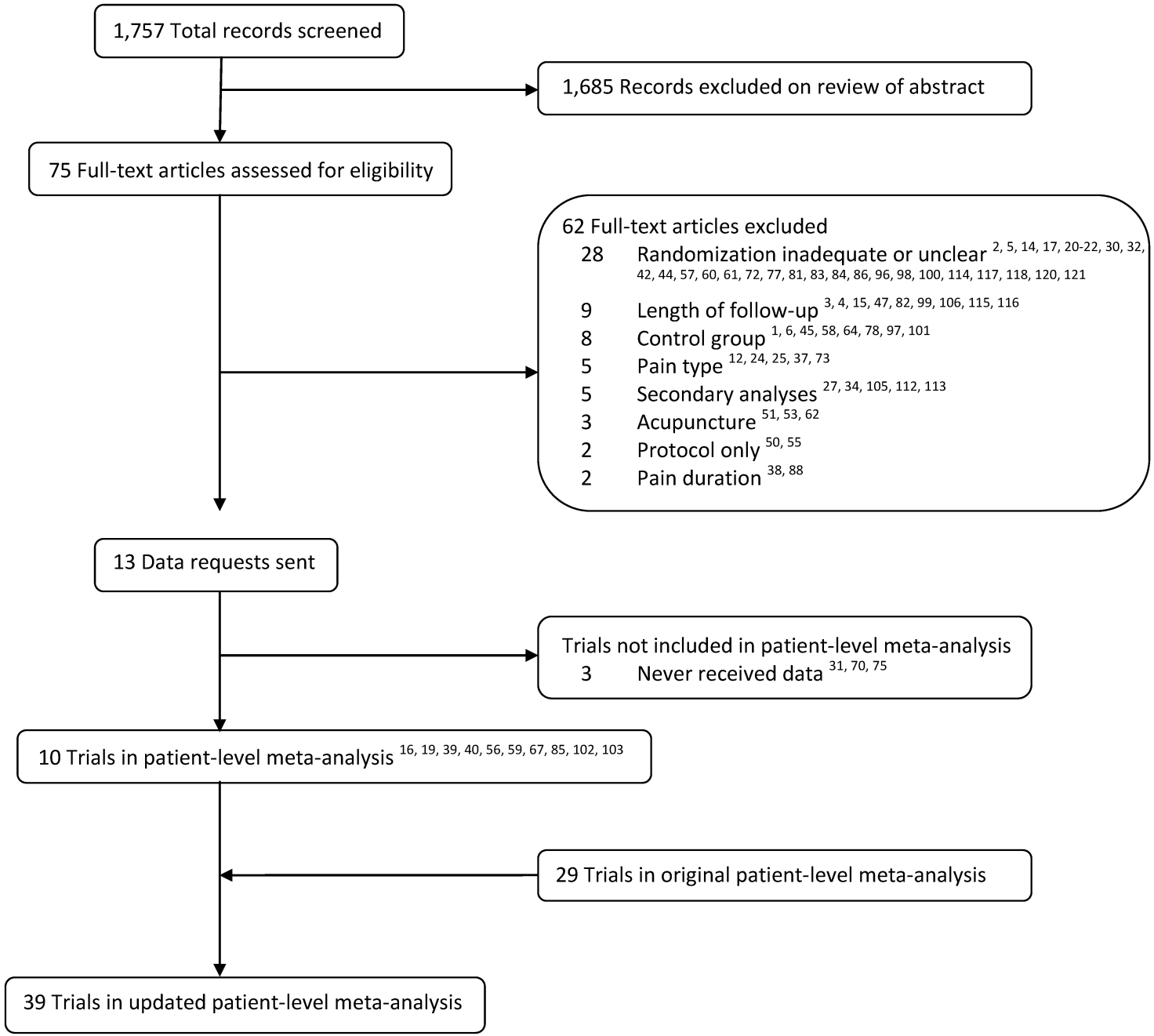
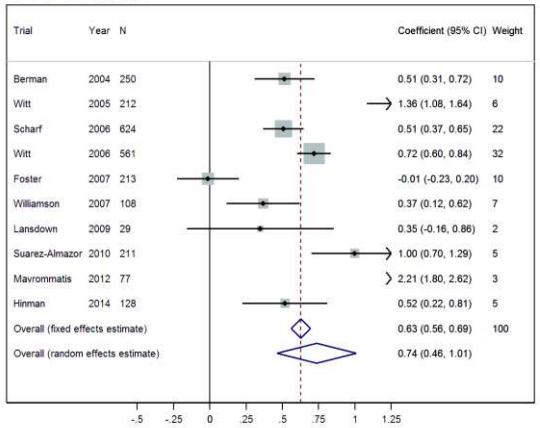
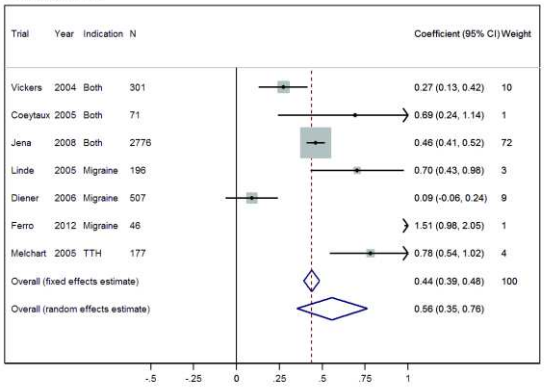


Figure 1 2017-10-24_bestsetConverted.png

Osteoarthritis



Headache



Musculoskeletal Pain

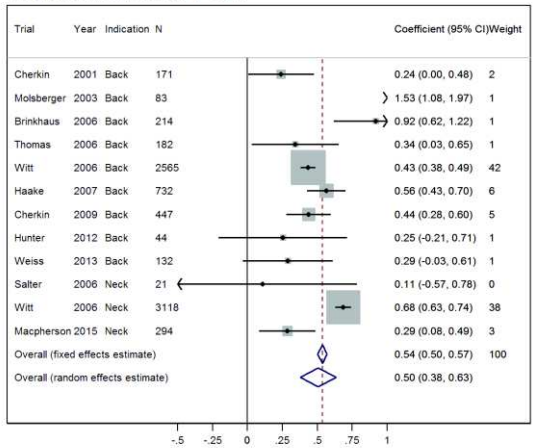
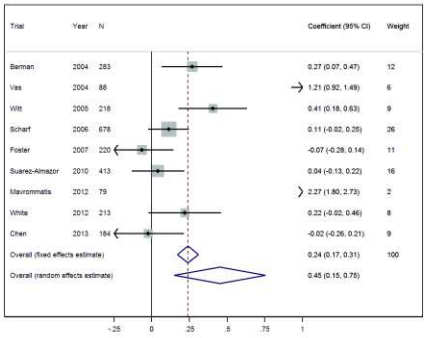
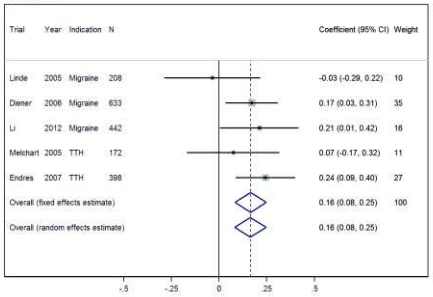


Figure 2 No Acupuncture Control.eps

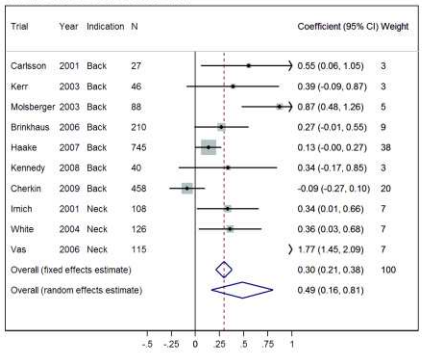
Osteoarthritis



Headache



Musculoskeletal Pain



Specific Shoulder Pain

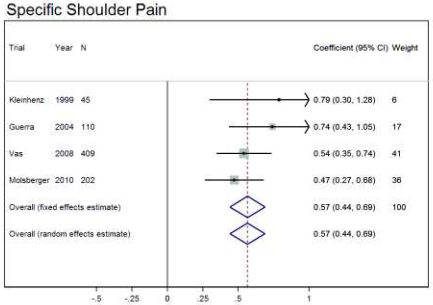


Figure 3 Sham Control.eps

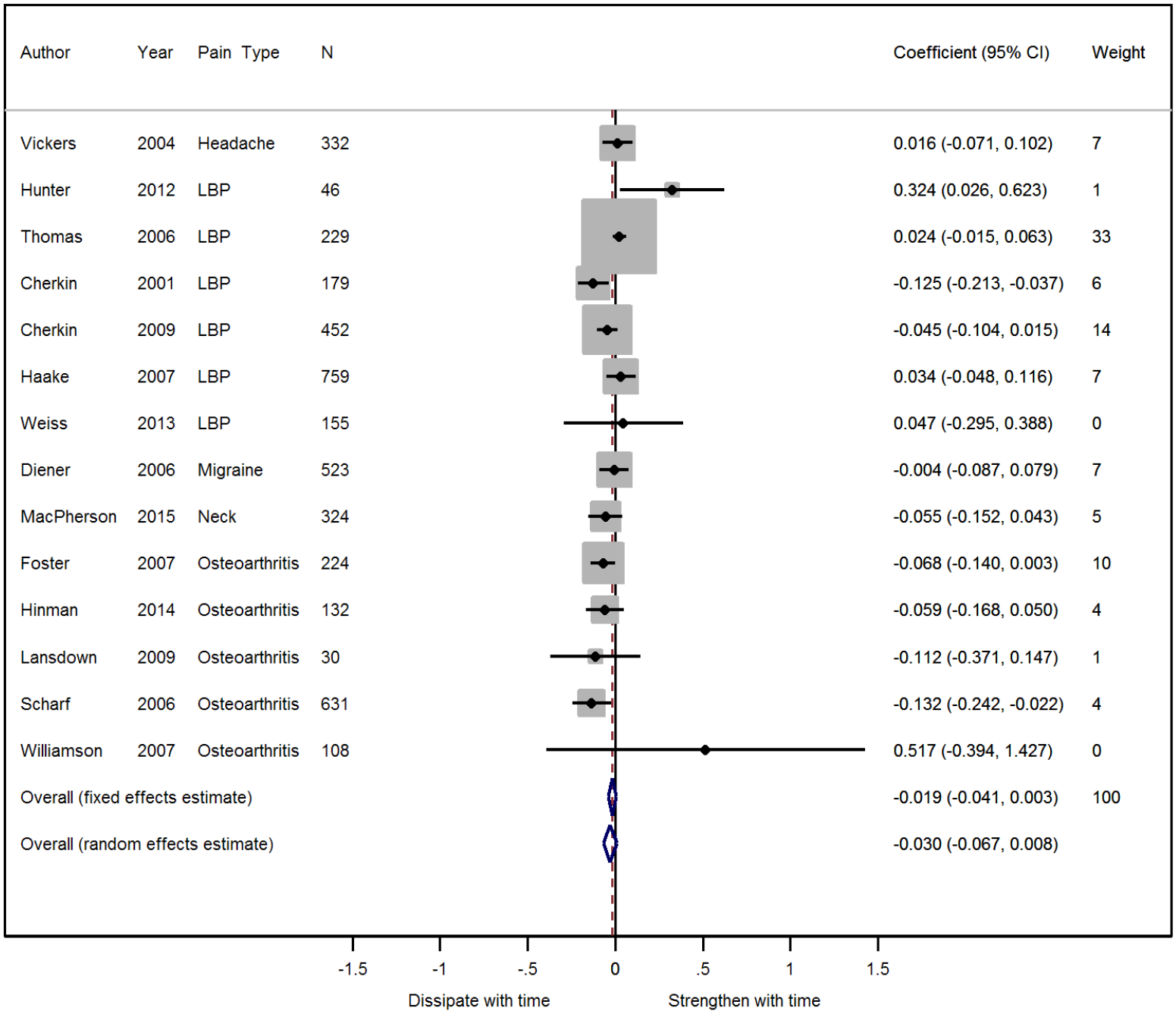


Figure 4a Time Course No Acupuncture.eps

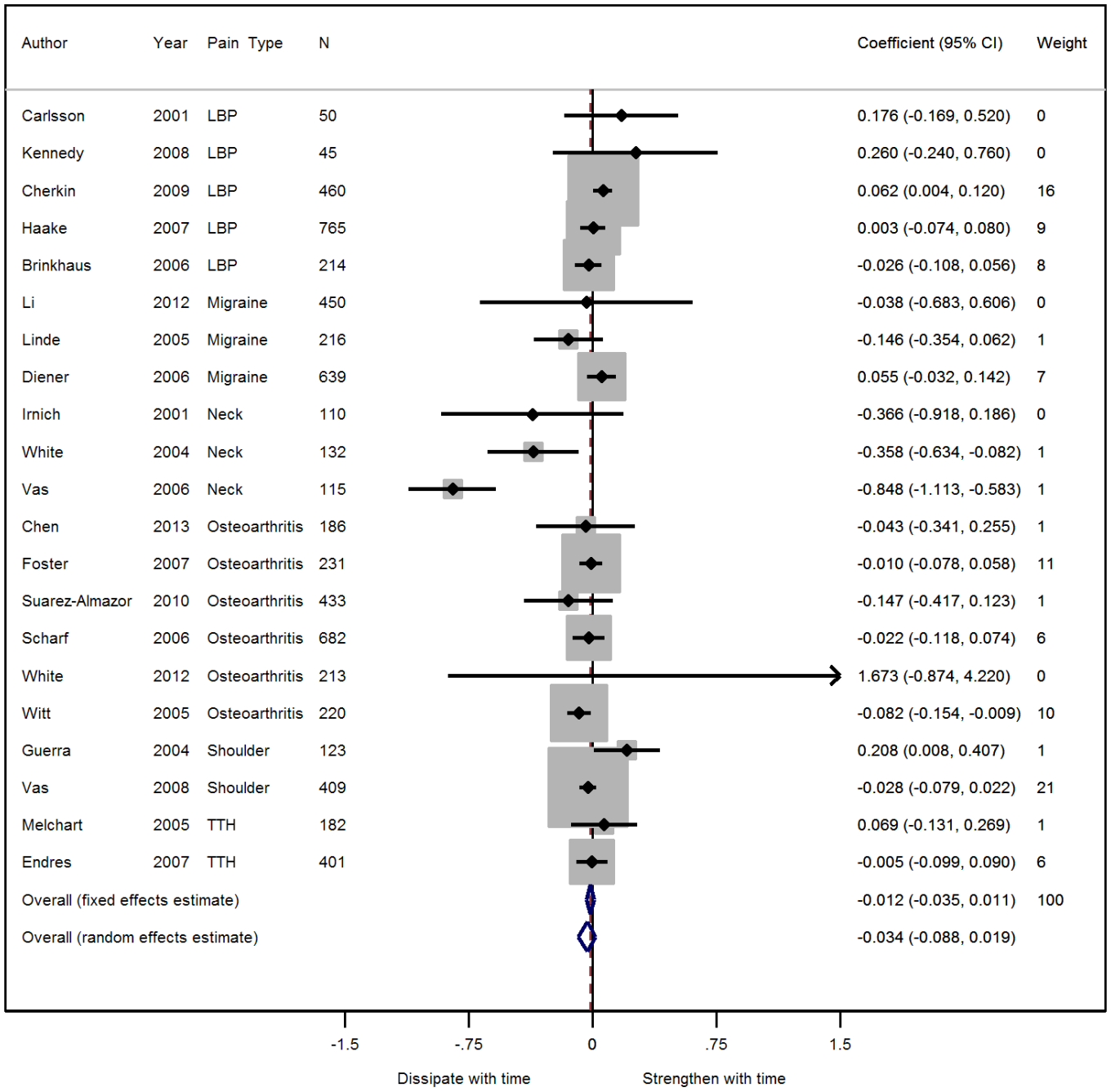
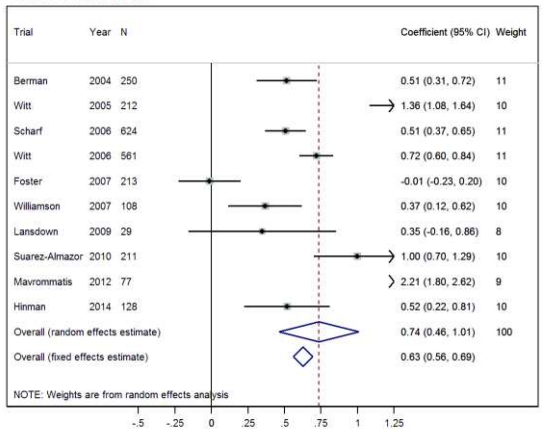
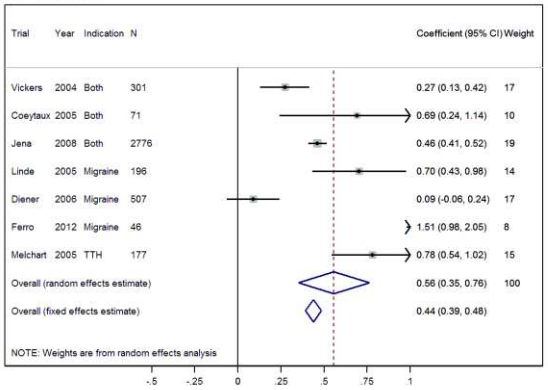


Figure 4b Time Course Sham.eps

Osteoarthritis



Headache



Musculoskeletal Pain

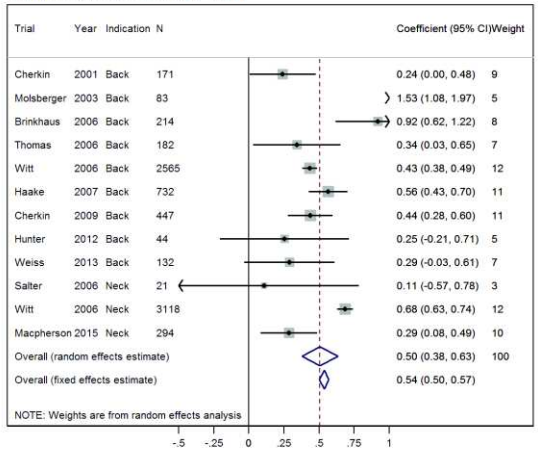
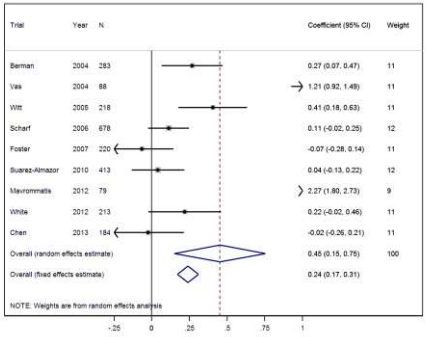
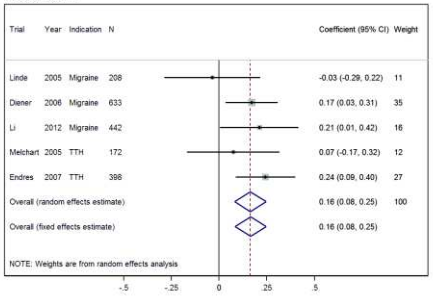


Figure S1 No Acupuncture Control RE.eps

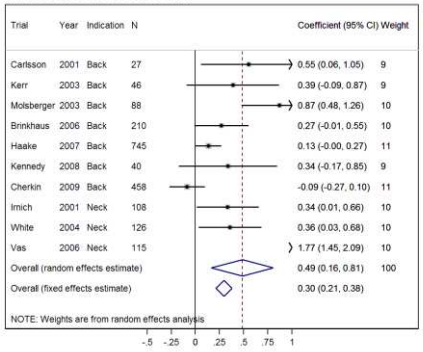
Osteoarthritis



Headache



Musculoskeletal Pain



Specific Shoulder Pain

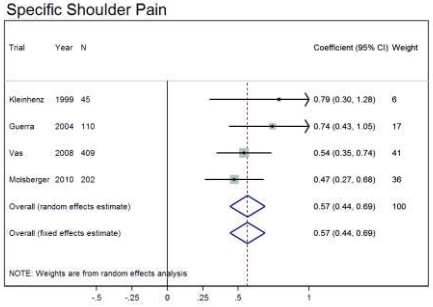


Figure S2 Sham Control RE.eps